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BANNER & WITCOFF, LTD.
1100 13th STREET, N.W.
SUITE 1200
WASHINGTON, DC 20005-4051

EXAMINER	
HILL, KEVIN KAI	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/656,140	TAO ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,10-13,16-22,24,25,34,62,64 and 66-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,10-13,16-22,24,25,34,62,64 and 66-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Amendments

1. Applicant's amendments to Claims 1, 5, 7, 11, 13, 17, 19 and 21 in the reply filed January 18, 2007 is acknowledged. Also acknowledged are Applicant's new claims, Claims 66-68, which have been entered into the application as requested and will be examined on the merits herein, as they are considered to belong to the elected group, Group I. Applicant has cancelled Claims 2-3, 8-9, 14-15, 45-61, 63 and 65.

Claims 1, 4-7, 10-13, 16-22, 24-25, 34, 62, 64 and 66-68 are under consideration.

Information Disclosure Statement

Applicant has filed an Information Disclosure Statement on January 18, 2007 that has been considered. The signed and initialed PTO Form 1449 is mailed with this action.

Claim Objections

2. **The prior objection to Claims 1, 7, 13, 19, 45-61 and 65 is withdrawn** because Applicant has either cancelled or amended the claim to address the relevant issue(s).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Claims 1, 4-7, 10-13, 16-22, 24-25, 34, 62 and 64 stand and Claims 66-68 are newly rejected under 35 U.S.C. 112, first paragraph,** as failing to comply with the written

description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-1111 (also available at www.uspto.gov).

The claimed invention is directed to methods for relieving acute or chronic pain, for treating or preventing hyperalgesia and for reducing a threshold for anesthesia, wherein the methods comprise the step of administering to a subject an agent that inhibits the expression of PSD95, and a claimed invention directed to a pharmaceutical formulation comprising an antisense polynucleotide that is complementary to PSD95 messenger RNA. When the claims are analyzed in light of the specification, instant invention recites/encompasses an expansive genus of structurally distinct compositions capable of inhibiting the expression of all known, and unknown, PSD95 genes encoded by all metazoans.

The lack of written support in the specification for the vast genus of agents that inhibit the expression of PSD95 will be addressed presently.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the antisense oligonucleotide of SEQ ID NO:1 that is complementary to nucleotides 241 to 258 of the rat PSD95 nucleotide sequence recorded in the

art as GenBank Accession No. M96853 (page 19, line 31; page 20, line 3) is the only species whose complete structure is disclosed. Applicant contemplates that the antisense oligonucleotide may be administered in a vector, a liposome, a particle or some other protective formulation (page 6, lines 18-20).

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that the antisense oligonucleotide be complementary to a nucleotide sequence encoding a PDZ domain (page 6, line 15). **In regard to antisense oligonucleotides complementary to PDZ domains or PSD95 messenger RNAs from species other than humans, it is noted that the specification does not provide any disclosure whether these sequences from other species would have had the same characteristics or would have had additional characteristics or properties.**

However, the specification does not disclose any identifying characteristic as to how an artisan would have differentiated an agent that inhibits the expression of PSD95 from any other agent that inhibits the expression of PSD95, how an artisan would have differentiated an antisense oligonucleotide complementary to a nucleotide sequence encoding a given PDZ domain from any other agent that inhibits the expression of PSD95, or how an artisan would have differentiated an antisense oligonucleotide complementary to a nucleotide sequence encoding the first PDZ domain of rat PSD95 from an antisense oligonucleotide complementary to a nucleotide sequence encoding the second or third PDZ domain(s) of rat PSD95. It is noted that although Applicant anticipates that an antisense oligonucleotide targeted to the third PDZ domain in PSD95 may be the most effective (page 7, line 8), that it is understood in the art that the second PSD95 PDZ domain is encoded by nucleotides 160 to 246 and that the third PSD95 PDZ domain is encoded by nucleotides 313 to 393 of the rat PSD95 nucleotide sequence recorded in the art as GenBank Accession No. M96853. Thus, the inventive antisense oligonucleotide of SEQ ID NO:1 is complementary to a nucleic acid encoding only a very small portion (two amino acids) of the second PDZ domain of the full length rat PSD95 protein.

With respect to the pharmaceutical composition comprising the antisense oligonucleotide, the specification does not disclose any identifying characteristics as to how an artisan would

have differentiated a given delivery vehicle, e.g. a plasmid vector, from any other delivery vehicle, e.g. a liposome, a virus particle or some other protective formulation. It is noted that all these agents, antisense oligonucleotides and delivery vehicle compositions vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

The Revised Interim Guidelines state, "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. ...In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Further, *Vas-cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-cath* at page 1116). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

The applicant has not provided any description or reduction to practice of administering a vector, liposome, particle or other protective formulation of a vast genus of antisense oligonucleotide agents that inhibits the expression of the genus of metazoan PSD95 genes. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of an antisense oligonucleotide sequence that is complementary to all possible metazoan PSD95 messenger RNAs that will inhibit expression of the PSD95 gene in any given metazoan and effect the desired therapeutic outcome, or the detailed chemical structure of the genus of agents encompassed by the claims. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The one agent species specifically disclosed, the antisense oligonucleotide of SEQ ID NO:1 that is complementary to nucleotides 241 to 258 of the rat PSD95 nucleotide sequence recorded in the art as GenBank Accession No. M96853, is not representative of the genus because the genus is highly variant. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.)

Accordingly, with respect to the claimed pharmaceutical composition, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the broad genus of pharmaceutical compositions comprising a broad genus of agents that inhibit the expression of all possible PSD95 genes, or a broad genus of antisense oligonucleotides complementary to all possible PDZ domains, or a broad genus of antisense oligonucleotides complementary to all possible PSD95 messenger RNAs, or a broad genus of antisense oligonucleotides complementary to all possible PSD95 PDZ domains, besides the formulation of naked antisense oligonucleotides of SEQ ID NO:1 that is complementary to nucleotides 241 to 258 of the rat PSD95 nucleotide sequence recorded in the art as GenBank Accession No. M96853, at the time the application was filed.

Accordingly, given that the one agent species specifically disclosed, the antisense oligonucleotide of SEQ ID NO:1 that is complementary to nucleotides 241 to 258 of the rat

PSD95 nucleotide sequence recorded in the art as GenBank Accession No. M96853, is not representative of the genus because the genus is highly variant, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the genus of required starting materials to perform the necessary active steps and effect the claimed method(s), at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph.

Applicant's Arguments

Applicant argues that the PSD95 mRNA of M96853 (rat) is highly representative of other PSD95 mRNAs. It is, for example, 96% identical to the mouse PSD95 mRNA, 94% identical to the dog PSD95 mRNA, and 93% identical to each of the human, the macaque, and the chimp PSD95 mRNAs.

Applicant's argument(s) has been fully considered, but is not persuasive.

Although Applicant contends that a BLAST alignment has been provided as evidence for the sequence similarities between PSD95 mRNAs across diverse mammalian organisms, the Examiner is unable to find the cited BLAST alignment in the papers filed.

The substantive issue is whether the single disclosed antisense oligonucleotide, the antisense oligonucleotide of SEQ ID NO:1 that is complementary to nucleotides 241 to 258 of the rat PSD95 nucleotide sequence recorded in the art as GenBank Accession No. M96853 (page 19, line 31; page 20, line 3), is representative of the enormous genus of antisense oligonucleotides directed against an enormous genus of mammalian subjects so as to perform the claimed inventive functions, specifically relieving acute or chronic pain, treating or preventing hyperalgesia and reducing a threshold for anesthesia. Applicant has not provided evidence to support the enormous genus of antisense nucleic acids to perform the required functions encompassed by the claims.

4. **Claims 1, 4-7, 10-13, 16-22, 24-25, 34, 62 and 64 stand and Claims 66-68 are newly rejected are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for methods for a) relieving acute or chronic pain, b) treating hyperalgesia, and c) reducing a threshold for anesthesia comprising the method step of intrathecal administration of a pharmaceutical composition comprising naked antisense oligonucleotides of SEQ ID NO:1 that is complementary to nucleotides 241 to 258 of GenBank Accession No. M96853 encoding the rat PSD95 protein, to a subject, wherein the subject is a rat, the method (c) further comprising the administration of an anesthetic agent, wherein the anesthetic agent is isoflurane, does not reasonably provide enablement for:

i) an enormous genus of agents that inhibit the expression of an enormous genus of PSD95 genes (see Claims 1, 7 and 13),

ii) an enormous genus of antisense oligonucleotides complementary to an enormous genus of nucleotides encoding a PDZ domain (see Claims 4, 10, 16 and 20),

iii) an enormous genus of antisense oligonucleotides complementary to an enormous genus of nucleotides encoding an enormous genus of PSD95 messenger RNAs (see Claims 3, 9, 15 and 19),

iv) an enormous genus of antisense oligonucleotides complementary to nucleotides encoding an enormous genus of carboxy-terminal PDZ domains of an enormous genus of PSD95 proteins (see Claim 21),

v) an enormous genus of carriers for an enormous genus of agents,

vi) an enormous genus of means or routes of administration of the pharmaceutical composition(s),

vii) an enormous genus of anesthetics (see Claims 34, 62 and 64),

viii) an enormous genus of subjects, and

ix) a method for preventing hyperalgesia.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with

these claims. The *in vivo* therapeutic use of the antisense nucleic acid molecules complementary to a portion PSD95 of the present invention will be assessed for enablement purposes.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

With respect to the agents, the claims are broad for encompassing a vast genus of structurally distinct agents that are capable of inhibiting the expression of an expansive genus of PSD95 genes by distinctly different mechanisms. When the claims are analyzed in light of the specification, the inventive concept in the instant application is the administration of antisense oligonucleotides complementary to a nucleotide sequence encoding the PSD95 protein. The specification teaches that an antisense oligonucleotide may be complementary to a genus of nucleotide sequences encoding a PDZ domain or may be complementary to a genus of messenger RNAs encoding a PSD95 protein (page 6, lines 14-16). Applicant contemplates that the antisense oligonucleotide may be administered in a vector, a liposome, a particle or some other protective formulation (page 6, lines 18-20).

With respect to the subject to whom the therapeutic agent(s) will be administered, the claims are broad for encompassing all metazoan subjects. When the claims are analyzed in light of the specification, the inventive concept of the instant invention is the treatment or amelioration of acute or chronic pain and for reducing the threshold for anesthesia in mammalian subjects, accomplished by intrathecal administration of the therapeutic antisense oligonucleotide. Applicant does not define "subject"; however, because Applicant contemplates the formulation of the inventive therapeutic agent to be manufactured under regulator-approved conditions for administration to humans (page 7, lines 14-15), one of ordinary skill in the art would reasonably conclude that Applicant contemplates the application of the inventive methods to include human subjects.

With respect to the method(s) of a) relieving acute or chronic pain, b) treating or preventing hyperalgesia, and c) reducing a threshold for anesthesia, the claims are broad for encompassing a vast genus of pathologies that are etiologically and symptomatically different and encompassing diverse means and routes of administering the therapeutic antisense oligonucleotide. Furthermore, method (c) is broad for encompassing all possible anesthetics. When the claims are analyzed in light of the specification, the methods are applied to a rat animal model and only the anesthetic isoflurane.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

With respect to antisense oligonucleotides complementary to a nucleotide sequence encoding a PDZ domain, the art teaches that PDZ-domain-containing proteins are numerous in all currently sequenced metazoan genomes (Harris and Lim, J. Cell Science 114: 3219-3231, 2001). For example, over 394 different PDZ domains have been found in humans. Proteins may contain as few as one PDZ domain (Veli1), three PDZ domains (PSD95) or even up to thirteen PDZ domains (MUPP1) (page 3223, Figure 4). Applicant anticipates that an antisense oligonucleotide targeted to the third PDZ domain in PSD95 may be the most effective (page 7, line 8). Stein (2000) teaches "[A]ntisense oligonucleotide biotechnology has entered a phase of its development in which many problems engendered by non-sequence specificity are being recognized and being actively addressed. However, in order to improve specificity of the

methodology, attention must now also be paid to co-suppression of gene activity due to irrelevant cleavage." Stein further states that "[T]o the extent that this issue also is addressed, correlations between the down-regulation of a defined target and an observed biological outcome (e.g., growth suppression) *eventually* [emphasis added] may be possible." (page 235, Concluding remarks) Stein clearly suggests that use of antisense oligonucleotide therapeutics are highly unpredictable due to "irrelevant cleavage" as a result of the low stringency requirements for RNAse H activity, wherein a 5-base complementary region of oligomer to target may be sufficient to elicit RNAse H activity (see Stein, abstract). Thus, the antisense oligonucleotide complementary to a nucleotide sequence encoding a PSD95 PDZ domain must not cross-react with all other nucleic acids encoding a PDZ domain.

With respect to the delivery of oligonucleotide pharmaceutical compositions *in vivo*, the state of the art indicates that delivery of these oligonucleotide compositions for therapeutic purposes "remains an important and inordinately difficult challenge (Chirila et a1, January, Biomaterials 23:321-342, 2002., see abstract)." Chirila et al. (page 327, last paragraph) teach that "(T)he *in vivo* delivery techniques chiefly used at the present, i.e. infusion or injection of naked molecules and liposomal systems, do not assure adequately long-term maintenance of ODNS (oligonucleotides) in tissues," which is required to achieve therapeutic effects. As a conclusion to the review of Chirila et al, the state of oligonucleotide based drug therapy is summarized by the statement: "the antisense strategy only awaits a suitable delivery system in order to live up to its promise." Therefore, the efficacy of antisense based therapies hinges upon the ability to deliver a sufficient amount of oligonucleotide, to the appropriate tissues, and for a sufficient period of time, to produce the desired therapeutic effect. So far, it appears that all of the developments in antisense-based therapies have not been sufficient to overcome this one basic obstacle, drug delivery.

Jen et al. (Stem Cells, Vol. 18: 307-319, 2000) provide a review of the challenges that remain before antisense-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress needs to be made. Moreover Jen et al. conclude that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained

elusive." It is also concluded that "[a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (See page 315, last two paragraphs).

Moreover, Chirila et al. (2002), Jen et al. (2000), and Stein (2000) teach that the behavior of oligonucleotide based compositions and their delivery *in vivo* are unpredictable, therefore claims to pharmaceutical compositions and methods of treating diseases by the administration of oligonucleotide based pharmaceuticals are subject to the question of enablement due to the high level of unpredictability associated with this technique as taught in the prior art.

With respect to the method(s) of a) relieving acute or chronic pain, b) treating or preventing hyperalgesia, and c) reducing a threshold for anesthesia by administering an antisense oligonucleotide to a nucleic acid sequence encoding PSD95, at the time of filing of the instant application there were no general guidelines for successful *in vivo* delivery of antisense compounds known in the art, nor are such guidelines provided in the specification as filed for the therapeutic treatment of pain in humans. Chizh and Headley (Curr. Pharm. Design 11(23): 2977-2994, 2005) teach that "[A]ll of the animal models developed to test compounds for neuropathic pain indications involve insults to peripheral nerves or central structures that are able to trigger neuropathic pain in man. However, the time-scales in these animal models are very different to clinical circumstances, with chronic pain in patients with neuropathy typically being of a substantially longer duration prior to the start of pharmacological treatment than in corresponding animal models (months or years *vs.* days or weeks). It is likely, therefore, that additional pathophysiological mechanisms may be involved under these chronic conditions in patients that cannot be invoked in animal models" (page 2984, column 1). Furthermore, "[T]here are currently no techniques for assessing ongoing pain in animals. The value of data on anti-hyperalgesic or anti-allodynic efficacy in animal models of neuropathic pain for predicting efficacy on spontaneous ongoing pain (the most important symptom in the majority of neuropathic pain patients) therefore remains uncertain".

Thus, despite the high degree of skill for one of ordinary artisan, the art recognizes considerable uncertainty in the predictability of antisense oligonucleotides to demonstrate target

specificity and demonstrate real-world, *in vivo* therapeutic efficacy. Similarly, the art recognizes considerable uncertainty in the predictability of an artificially manipulated animal model to reflect real world etiologically and symptomatically distinct human neuropathologies.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

With respect to agents that inhibit the expression of PSD95, the specification teaches only the use of an antisense oligonucleotide of SEQ ID NO:1 that is complementary to nucleotides 241 to 258 of the rat PSD95 nucleotide sequence recorded in the art as GenBank Accession No. M96853. It is noted that although Applicant anticipates that an antisense oligonucleotide targeted to the third PDZ domain in PSD95 may be the most effective (page 7, line 8), that it is understood in the art that the second PSD95 PDZ domain is encoded by nucleotides 160 to 246 and that the third PSD95 PDZ domain is encoded by nucleotides 313 to 393 of the rat PSD95 nucleotide sequence recorded in the art as GenBank Accession No. M96853. Thus, the inventive antisense oligonucleotide of SEQ ID NO:1 is complementary to a nucleic acid encoding only a very small portion (two amino acids) of the second PDZ domain of the full length rat PSD95 protein.

Applicant also contemplates that the antisense oligonucleotide may be administered in a vector, a liposome, a particle or some other protective formulation; however, the working examples only guide an artisan to administer naked antisense oligonucleotides in saline.

With respect to the method(s) of a) relieving acute or chronic pain, b) treating or preventing hyperalgesia, and c) reducing a threshold for anesthesia by administering a naked antisense oligonucleotides dissolved in saline and administered intrathecally, that is via intraspinal catheter, the working examples teach the efficacy of the inventive antisense oligonucleotide of SEQ ID NO:1 as applied only to the rat animal model under acute, short-term (less than two weeks) settings to a) relieve acute pain (Example 9) and chronic pain (Example 12), b) treat, but not prevent, thermal hyperalgesia (Example 1), and c) decrease in threshold for isoflurane (Examples 5-6). The Example 1 discloses that the tail-flick response was reduced, but not prevented in rats pre-treated with anti-sense oligonucleotides (page 12). However, the specification does not teach several important considerations. For instance, the specification does

not teach working examples of any other antisense oligonucleotide complementary to any other part of a nucleic acid messenger RNA encoding the rat PSD95 protein, nor any other messenger RNAs encoding other PSD95 mammalian family members. The specification also does not teach the administration of the inventive antisense oligonucleotide of SEQ ID NO:1 by any other means to the spinal cord or to any other tissue. The specification does not teach an artisan how to deliver a sufficient amount of oligonucleotide, to any appropriate tissue(s), and for a sufficient period of time, to produce the desired therapeutic effect by any means other than intrathecal administration to the spinal cord. The specification also does not teach the ability of the inventive antisense oligonucleotide of SEQ ID NO:1 to decrease in threshold for any other anesthetic.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that: an enormous genus of antisense oligonucleotides complementary to an enormous genus of nucleotides encoding a PDZ domain, an enormous genus of agents that inhibit the expression of an enormous genus of PSD95 genes, an enormous genus of antisense oligonucleotides complementary to an enormous genus of nucleotides encoding an enormous genus of PSD95 messenger RNAs, an enormous genus of antisense oligonucleotides complementary to nucleotides encoding an enormous genus of carboxy-terminal PDZ domains of an enormous genus of PSD95 proteins may be formulated with an enormous genus of carriers for an enormous genus of agents for administration to an enormous genus of metazoan subjects, to a) relieve acute or chronic pain, b) treat or prevent hyperalgesia, and c) reduce a threshold for an enormous genus of anesthetics.

Therefore, the specification does not describe the use of an enormous genus of antisense oligonucleotides as an inhibitor of PDS95 for the *in vivo* treatment or prevention of a neuropathic disease or condition in an enormous genus of mammalian subjects in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. This conclusion is based upon the known unpredictability regarding the delivery of antisense *in vivo*, the behavior of an antisense compound in a cell, the art-recognized uncertainty in the predictability of an artificially manipulated animal model to reflect real world

etiologically and symptomatically distinct human neuropathologies, and the lack of guidance in the specification as filed in this regard.

The quantity of experimentation required to practice the invention in any metazoan subject other than a rat as claimed would require determining modes of delivery in any metazoan patient other than a rat such that a single gene is inhibited and the desired secondary effect, that is treatment leading to the amelioration of conditions, specifically, acute or chronic pain, hyperalgesia, and a reduced threshold for all possible anesthetics, associated with the expression of PSD95 in any metazoan patient other than a rat, is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to methods for a) relieving acute or chronic pain, b) treating hyperalgesia, and c) reducing a threshold for anesthesia comprising the method step of intrathecal administration of a pharmaceutical composition comprising naked antisense oligonucleotides of SEQ ID NO:1 that is complementary to nucleotides 241 to 258 of GenBank Accession No. M96853 encoding the rat PSD95 protein, to a subject, wherein the subject is a rat, the method (c) further comprising the administration of an anesthetic agent, wherein the anesthetic agent is isoflurane, is proper.

Applicant's Arguments

Applicant argues that:

a) the neither the genus of PSD95 mRNAs, nor the genus of PSD95 PDZ domains are not "enormous",

b) the subject must be one who has "acute or chronic pain",

c) the subject must be one who is prone to develop hyperalgesia,

d) the subject must be one to which anesthesia is administered,

e) the specification need not teach, and preferably omits, what is well known in the art, regarding the enormous genus of means and routes to administer the inventive antisense oligonucleotide, as such methods are well known in the art, and
f) perfection is not required for enablement to deliver antisense oligonucleotides.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), the Examiner respectfully reminds Applicant that the genome of the fruit fly, *Drosophila melanogaster*, encodes a PSD95 homologue (Wheal et al, Progress in Neurobiology 55(6):611-640, 1998; pg 627, col. 1, Section 5, lines 30-32; Stathakis et al, Genomics 44(1): 71-82, 1997, pg 80, Figure 5), wherein "PSD-95 is homologous to the *Drosophila* tumor suppressor protein, Dlg, in both sequence and structural organization." The instant specification does not explicitly exclude PSD95 homologues extant in organisms other than rats and humans, for example. Thus, it is the Examiner's position that the genus of PSD95 mRNAs and the genus of PSD95 PDZ domains are each, respectively "enormous".

With respect to b), Applicant does not define the "subject" to whom the oligonucleotide will be administered, and thus the breadth of the claims reasonably encompass all animals extant at this time in the biological world, both vertebrate and invertebrate. Applicant provides no evidence that non-mammalian metazoans do not experience acute or chronic pain. Rather, the Examiner reminds Applicants that laboratory animals are routinely used in the art for research to better understand the physiology of pain, and therapies thereof (Manev et al, Life Sciences 76(21): 2403-2407, 2005).

With respect to c), the limitation of developing hyperalgesia is independent of Claim 1 and 13. Although hyperalgesia may only exist in mammalian organisms, the genus of mammalian organisms extant at this time in the biological world is enormous. The instant mammalian genus reasonably encompasses some 5,500 species (including humans), distributed in about 1,200 genera, 152 families and up to 46 orders (en.wikipedia.org/wiki/Mammal, last visited March 21, 2007).

With respect to d), Applicant is reminded that anesthesia is administered to laboratory animals, including the fruit fly *Drosophila melanogaster*. In particular, Applicant is referred to

van Swinderen (J. Neurobiology 66(11): 1195-1211, 2006; Abstract only) who teaches the administration of isoflurane to *Drosophila.*

With respect to e), although the means and routes by which an artisan may deliver a nucleic acid to a subject has been formally recognized as possibilities, the substantive issue is whether the instant inventive antisense oligonucleotide can perform the claimed therapeutic treatments as per the means encompassed by the claims. In addition to recognizing the possible administration means and method steps, the art also recognizes significant obstacles and unpredictability, as discussed in the cited art. Applicant has provided no evidence that their inventive composition is capable of performing the claimed methods by any other means than the intrathecal administration of naked nucleic acid.

With respect to f), the cited references do not teach the administration of the instant nucleic acid to treat the instantly claimed disease states, which is the substantive issue of the instant rejection. Applicant has provided no evidence that one of ordinary skill in the art could reasonably predict the therapeutic activity of the instant antisense oligonucleotide in the enormous genus of subjects embraced by the claims based upon the administration of unrelated nucleic acid molecules that target unrelated gene products that function in unrelated physiological and cell biological and signaling pathways.

MPEP §2164.06(b) Examples of Enablement Issues, Decisions Ruling that the Disclosure was Nonenabling

(A) In *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999), the court held that claims in two patents directed to genetic antisense technology (which aims to control gene expression in a particular organism), were invalid because the breadth of enablement was not commensurate in scope with the claims. Both specifications disclosed applying antisense technology in regulating three genes in *E. coli*. Despite the limited disclosures, the specifications asserted that the "[t]he practices of this invention are generally applicable with respect to any organism containing genetic material which is capable of being expressed ... such as bacteria, yeast, and other cellular organisms." The claims of the patents encompassed application of antisense methodology in a broad range of organisms. Ultimately, the court relied on the fact that (1) the amount of direction presented and the number of working

examples provided in the specification were very narrow compared to the wide breadth of the claims at issue, (2) antisense gene technology was highly unpredictable, and (3) the amount of experimentation required to adapt the practice of creating antisense DNA from *E. coli* to other types of cells was quite high, especially in light of the record, which included notable examples of the inventor's own failures to control the expression of other genes in *E. coli* and other types of cells. Thus, the teachings set forth in the specification provided no more than a "plan" or "invitation" for those of skill in the art to experiment using the technology in other types of cells.

The Examiner agrees with Applicant that "the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fischer*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). However, for the reasons discussed above, the instant disclosure teaching the use of a single antisense oligonucleotide administered intrathecally as a naked nucleic acid to a rat does not fully support the scope of the instantly recited claims. Applicant simply has not provided the necessary evidence to fully support the breadth of the claimed invention.

Claim Rejections - 35 USC § 112

5. **The prior rejection of Claims 4, 10, 16 and 21 under 35 U.S.C. 112, second paragraph is withdrawn** because Applicant has either cancelled or amended the claim to address the relevant issue(s).

Conclusion

6. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kevin K. Hill

Q. JANICE LI, M.D.
PRIMARY EXAMINER